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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,135	07/25/2001	Hajime Matsuzaki	3414	8220

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,135	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *37-49,55 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36 and 50-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-36 and 50-54 in the paper filed May 28, 2004 is acknowledged.

Specification

2. The disclosure is objected to because of the following informalities:

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 19, lines 19 and 21, for example.

Appropriate correction is required.

Claim Interpretation

4. With regard to claims 3-5, the claims require that the ends are complementary. However, the claim is broad enough to permit two different interpretations. The first is that there is some common sequence so that the 5' end of the first strand could, for example, hybridize to the 3' end of the second strand. Sorge's adaptor sequence would inherently permit such a hybridization based upon the region of identity in the sequence (since the adaptor will be filled in during PCR). The second interpretation is that a hairpin is formed. The 103 rejection is written to address this alternative interpretation.

Information Disclosure Statement

5. The information disclosure statement filed July 30, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each

publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The remaining IDS forms included references and were considered.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-6, 10, 15-19, 24-36 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Sorge et al (U.S. Patent 6,060,245).

Sorge teaches a method of claim 1 and 50 comprising:

(a) fragmenting a first nucleic acid sample to produce fragments (see figure 1a, where the target and driver cDNA are cleaved with restriction enzyme R as well as example 1, column 46, lines 48-60, where the DNA was digested with AluI (a four base cutter)),

(b) ligating one or more adaptors to the fragments (see figure 1a, where adaptor pairs are ligated to the cleaved DNA and example 1, column 48, lines 55-67),

(c) amplifying a plurality of the fragments by PCR (see figure 1c and example 1, column 54, lines 6-12),

(d) where various conditions were modulated such as the optimal concentration of the nucleotide analogue methyl d-CTP in the PCR reaction (see column 51, lines 28-40), as well as the number of cycles of PCR (see column 52, lines 51-54).

With regard to claim 2, Sorge modulates the concentration of nucleotide analogues such as methyl d-CTP in the PCR reaction (see column 51, lines 28-40).

With regard to claim 3, Sorge teaches the adaptors at tables 2 and 3 (Column 49) and there is some level complementarity (For example, both adaptors share a sequence CTCTTCGAAGAGGAC, so that the ends would have some complementary sequence with one strand of one end being complementary to the other strand at the other end).

With regard to claims 4-5, the complementarity shown above is more than 10 basepairs long and is within 5 nucleotides of the ends after ligation of the adaptors (see column 49).

With regard to claim 6, Sorge expressly teaches optimization of PCR conditions including extension times (see column 73, line 63 to column 74, line 17).

With regard to claim 10, Sorge expressly teaches optimization of PCR conditions including primer concentration (see column 73, line 63 to column 74, line 17).

With regard to claims 15 and 50, Sorge expressly teaches optimization of PCR conditions including primer concentration (see column 73, line 63 to column 74, line 17).

With regard to claims 16-18, Sorge further teaches primers whose length are 20 nucleotides (see column 51, table 4, line 11).

With regard to claim 19, Sorge teaches some samples were nuclease treated (see column 55, lines 49-65).

With regard to claim 24, Sorge teaches the use of gel filtration (see column 56, lines 59-61).

With regard to claims 25 and 26, Sorge teaches the use of six base cutters (see column 55, line 12, EcoRI is a six base cutter).

With regard to claim 27, Sorge teaches adaptors which comprise PCR primers (see column 51, table 4).

With regard to claims 28-32, Sorge teaches in example 1 a second nucleic acid sample which retains about 50% of the starting material (see column 47, table 1).

With regard to claim 33, Sorge teaches the use of mRNA and cDNA as well as genomic DNA (See column 57, example 2 and column 58).

With regard to claims 34-36, Sorge teaches PCR of fragments from as small as 7 bp to as large as 1489 bp with a variety of intermediate sizes (see column 50, lines 55-57).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 7-9, 11-14 and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorge et al (U.S. Patent 6,060,245).

Sorge teaches a method of claim 1 and 50 comprising:

(a) fragmenting a first nucleic acid sample to produce fragments (see figure 1a, where the target and driver cDNA are cleaved with restriction enzyme R as well as example 1, column 46, lines 48-60, where the DNA was digested with AluI (a four base cutter)),

(b) ligating one or more adaptors to the fragments (see figure 1a, where adaptor pairs are ligated to the cleaved DNA and example 1, column 48, lines 55-67),

(c) digesting the fragments to produce single stranded "half" molecules (see figure 1c, cleave with Eam11041 and single stranded nuclease and example 1, column 54, lines 1-7),

(d) amplifying a plurality of the fragments by PCR (see figure 1c and example 1, column 54, lines 6-12),

(e) where various conditions were modulated such as the optimal concentration of the nucleotide analogue methyl d-CTP in the PCR reaction (see column 51, lines 28-40), as well as the number of cycles of PCR (see column 52, lines 51-54).

With regard to the limitation in claim 1 that the digestion create "half" fragments, this term is not defined in the specification in any limiting way. Consequently, any two fragments are "substantially" equal for the purposes of this rejection. In a particular case Eam11041 forms two products from a 710 nucleotide sequence of 443 and 267 nucleotides. These two fragments are each "substantially" half of 710 at 62% and 38% respectively. Also see column 47, where a 118 nucleotide sequence was cut into a 60 and 58 nucleotide pieces.

With regard to claim 2, Sorge modulates the concentration of nucleotide analogues such as methyl d-CTP in the PCR reaction (see column 51, lines 28-40).

With regard to claim 6, Sorge expressly teaches optimization of PCR conditions including extension times (see column 73, line 63 to column 74, line 17).

With regard to claim 10, Sorge expressly teaches optimization of PCR conditions including primer concentration (see column 73, line 63 to column 74, line 17).

With regard to claims 15 and 51, Sorge expressly teaches optimization of PCR conditions including primer concentration (see column 73, line 63 to column 74, line 17).

With regard to claims 16-18, Sorge further teaches primers whose length is 20 nucleotides (see column 51, table 4, line 11).

With regard to claim 19, Sorge teaches some samples were nuclease treated (see column 55, lines 49-65).

With regard to claim 24, Sorge teaches the use of gel filtration (see column 56, lines 59-61).

With regard to claims 25 and 26, Sorge teaches the use of six base cutters (see column 55, line 12, EcoRI is a six base cutter).

With regard to claim 27, Sorge teaches adaptors which comprise PCR primers (see column 51, table 4).

With regard to claims 28-32, Sorge teaches in example 1 a second nucleic acid sample which retains about 50% of the starting material (see column 47, table 1).

With regard to claim 33, Sorge teaches the use of mRNA and cDNA as well as genomic DNA (See column 57, example 2 and column 58).

With regard to claims 34-36, Sorge teaches PCR of fragments from as small as 7 bp to as large as 1489 bp with a variety of intermediate sizes (see column 50, lines 55-57).

Sorge does not teach the specific primer concentrations or extension times listed in the claims.

However, Sorge does expressly teach the optimization of these concentrations and extension times (see column 73, line 63 to column 74, line 17).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify Sorge to optimize the concentrations and times since Sorge expressly suggests such an optimization. Also, an ordinary practitioner

would have recognized that the results optimizable variables of extension time, and primer concentration could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times or primer concentrations for amplification was other than routine or that the results should be considered unexpected in any way as compared to the closest prior art.

11. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorge et al (U.S. Patent 6,060,245) in view of Shagin et al (Nucleic Acids Research (1999) 27(18) e23-25.

Sorge et al (U.S. Patent 6,060,245) teaches and suggests the limitations of claims 1, 2, 6-19, 24-36 and 51-55 as discussed above. Sorge does not teach the use of adaptors designed for formation of hairpins.

Shagin teaches using adaptors which will permit the 5' and 3' ends to be complementary to one another (see page e23, figure 1). With regard to claims 4 and 5, Shagin teaches adaptors which are more than 10 bases long and within 50 bases of the fragment ends (see page e23, figure 1 and figure 2a).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Sorge in the subtraction assay to take advantage of the primer method of Shagin since Shagin notes that the method will

"allow one to regulate the average length of the complex PCR product over a very wide range to make it most suitable for further manipulations (see abstract)". This directly addresses the concern of Sorge in optimizing conditions dependent upon the length and complexity of the sequences (see column 74, lines 14-17). Thus, an ordinary practitioner, motivated by Sorge to optimize length in complex DNA templates, would have been motivated by Shagin to use the Shagin method in order to regulate the length to the length desired for the further manipulations desired by Sorge.

12. Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorge et al (U.S. Patent 6,060,245) in view of Sorge et al (U.S. 2002/0119448 A1).

Sorge et al (U.S. Patent 6,060,245) teaches and suggests the limitations of claims 1, 2, 6-19, 24-36 and 51-55 as discussed above. Sorge does not teach the use of ddNTPs in the PCR reaction.

Sorge et al (U.S. 2002/0119448 A1) teaches that one way to limit enrichment to a selected area of a genome is by inclusion of a chosen concentration of chain terminating nucleotides such as dideoxynucleotides (see page 25, paragraph 369).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid selection method of Sorge et al (U.S. Patent 6,060,245) as taught by the later Sorge et al (U.S. 2002/0119448 A1) publication which suggests using ddNTPs in limiting enrichment to selected regions since Sorge et al (U.S. 2002/0119448 A1) states "In order to generate an enriched subportion of the genome by this method, the extension must be limited to avoid the theoretical replication of the entire genome, which would not enrich for sequences near

the sites recognized by the sequence-specific cleavage agent. One way to limit the length of the extension products is to include a chosen concentration of chain-terminating nucleotide analogs (such as dideoxynucleotides) to the extension mix (see page 25, paragraph 369)." An ordinary practitioner would have been motivated to modify the method of Sorge et al (U.S. Patent 6,060,245) to use the dideoxynucleotides in order to achieve an enriched subportion of the genome, where necessary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637

7/11/04